Table 5. Results obtained by AMINE for the four "unknown" amines.

Amine (prefix only)	Conditions: DELTA (ppm)	Conditions: Tallies used?	Solutions (prefix only)	Rank
N-(3-methylbutyl)-1,5-dimethylhexyl	1.5	no	N-(3-methylbutyl)-1,5-dimethylhexyl	-
N-(3-methylbutyl)-2-ethylhexyl	1.5	no	N-(3-methylbutyl)-2-ethylhexyl	-
N-heptyl-N-(3-methylbutyl)-2-ethylhexyl	1.5	yes	N-heptyl-N-(3-methylbutyl)-2-ethylhexyl	1 (tied)
			N-pentyl-N-(3-methylbutyl)-2-ethylhexyl	1 (tied)
N-pentyl-N-(3,3-dimethylbutyl)-3,5,5-trimethylhexyl	2.25[a]	yes	2-ethyl-1,5,5,7,7-pentamethyl-1-(2,2-dimethylpropyl)octyl	1
			N-pentyl-N-(3,3-dimethylbutyl)-3,5,5-trimethylhexyl	2 (tied)
			N,N-di(tert-butyl)-2-methyl-2-(2,2-dimethylpropyl)hexyl	2 (tied)
			N-tert-butyl-1,1,3-trimethyl-3-(2,2-dimethylpropyl)octyl	2 (tied)
			2-ethyl-1,1,5,7,7-pentamethyl-5-(2,2-dimethylpropyl)octyl	2 (tied)

a) With DELTA = 1.5 ppm, no structrures were found for this amine.

Figure captions

Figure 1. A schematic illustration of R, the alkyl chain-end to be tested by the PRUNER. The group X contains the Nitrogen atom, along with any carbons and hydrogens not included in R.

Figure 2. The hierarchy of pre-tests used by the PRUNER. A "?" attached to an atom indicates that the neighbors of that atom are unknown at testing time.

Figure 3. A case in which r and o do not match when $n = N_c$, even though the simple test is passed.

Figure 4. Sample output from program AMINE (PDP-10 version). The solution structure is written in polish-prefix notation as described in Reference 3a.

Figure 1

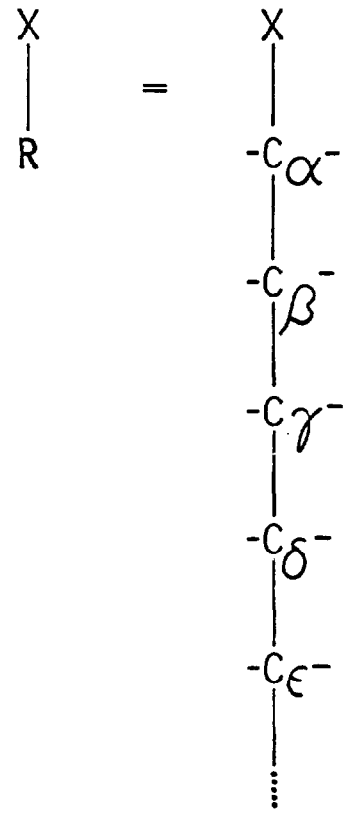


Figure 2.

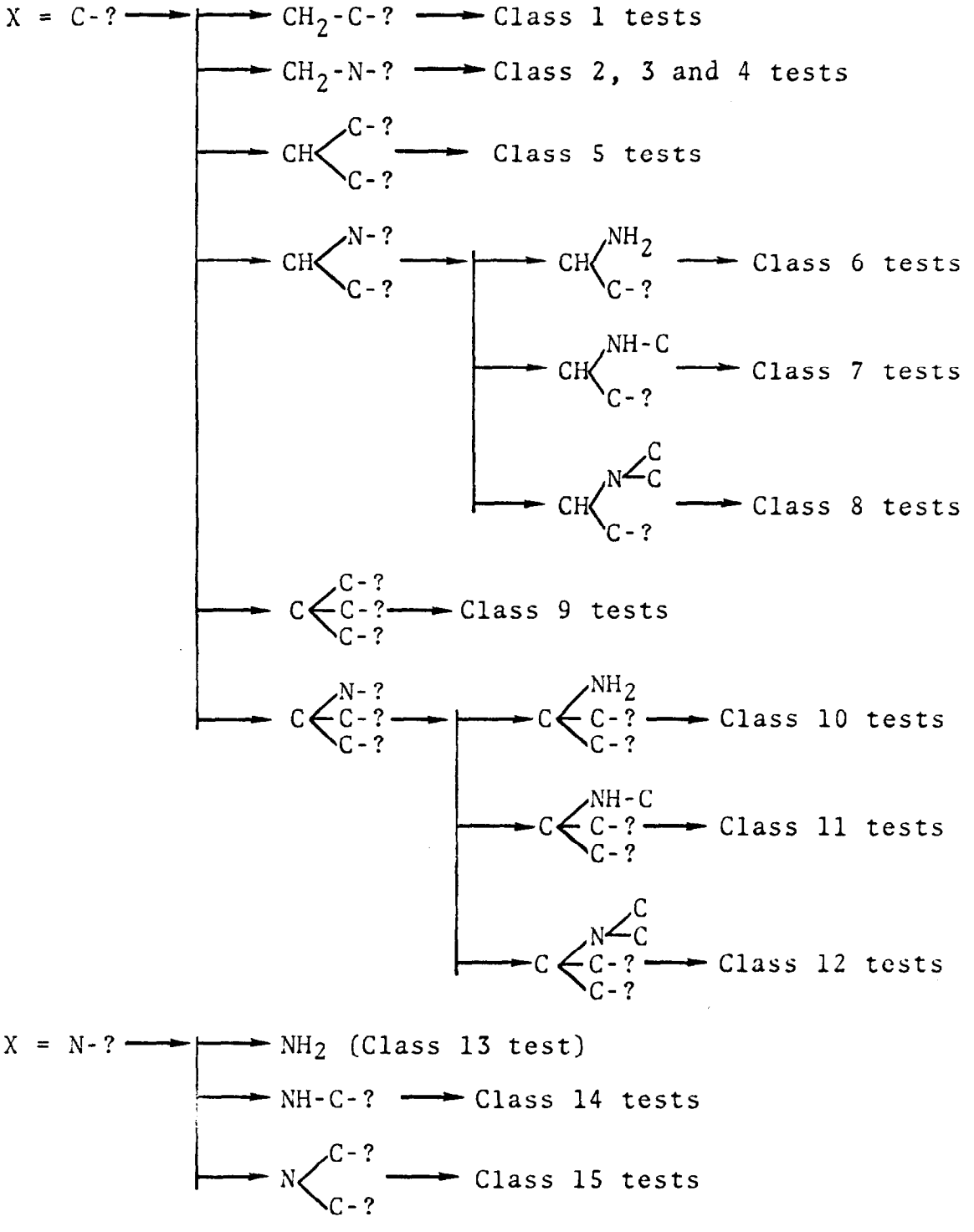
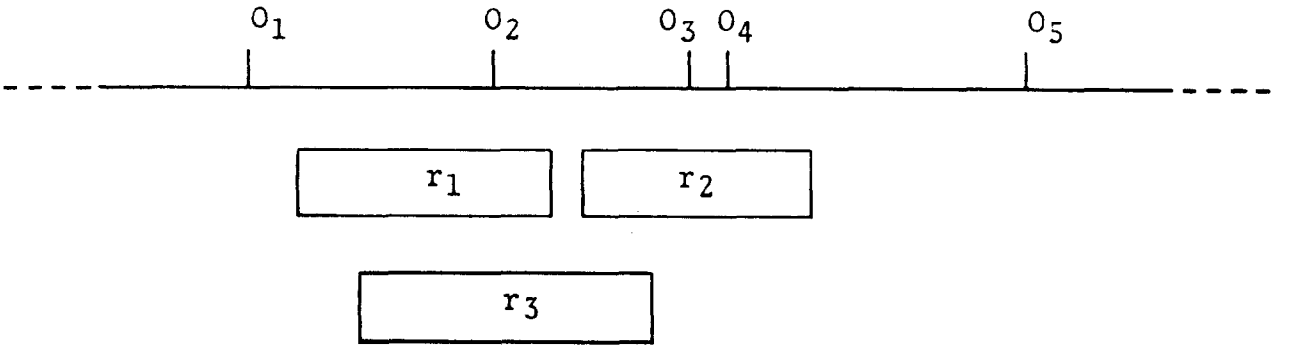

X = C-?
CH2-C-?
Class 1 tests
CH2-N-?
Class 2, 3 and 4 tests
CH(C-?)(C-?)
Class 5 tests
CH(N-?)(C-?)
CH(NH2)(C-?)
Class 6 tests
CH(NH-C)(C-?)
Class 7 tests
CH(N(C)C)(C-?)
Class 8 tests
C(C-?)(C-?)(C-?)
Class 9 tests
C(N-?)(C-?)(C-?)
C(NH2)(C-?)(C-?)
Class 10 tests
C(NH-C)(C-?)(C-?)
Class 11 tests
C(N(C)C)(C-?)(C-?)
Class 12 tests
X = N-?
NH2 (Class 13 test)
NH-C-?
Class 14 tests
N(C-?)(C-?)
Class 15 tests

Figure 3.



```
CASE TITLE:  N-ETYLYDIPENTYLAMINE
THE AMINE HAS 12 CARBONS
GOODNESS-OF-FIT CRITERION IS  1.500
STANDARD IS TMS
INPUT SHIFTS:   54.00  27.80  30.10  23.00  14.30  47.8

SOLUTION STRUCTURES:

N...C.C.C.C.CC.C.C.C.CC.C
SHIFTS:   54.299  27.881  30.239  22.960  14.210  54.29
          27.881  30.239  22.960  14.210  47.667  12.86
DELMIN =  0.37

CASE FINISHED.  PROCESSING TIME (IN SEC.) WAS    9.711
```

SIGNIFICANCE

SIGNIFICANCE

Because of the interdisciplinary character of this research, it has a significant impact in medicine, organic chemistry, and computer science. GC/MS has become one of the most powerful techniques available to the organic and biochemist. The potential applications of these techniques in medical research and in the clinic have just begun to be explored. These techniques are of unique importance to medical science since they alone of the current physical methods have sufficient sensitivity and analytical precision to study human biochemistry at the molecular level. Computer automation of these techniques, both at the instrumentation and interpretive levels, would permit the rapid, exhaustive analysis of body fluids across large populations of individuals in various medical contexts and may provide new discoveries important to public health.

In our study of errors of metabolism, accurate diagnosis of the accumulated metabolite provides insight into the biochemical pathogenesis and into therapeutic approaches to the control of such errors. In the case of inherited errors, accurate diagnosis allows reference to published data on the mode of inheritance and, thus, expresses the recurrence risk for genetic counseling purposes. The GC/MS system, with its potential for identification of any metabolites, provides the diagnostic accuracy necessary for a clinical program. GC/MS also provides the methodology for detecting previously unrecognized metabolic errors.

From the point of view of computer science, mass spectrometry is an advantageous environment in which to investigate the concepts necessary for the emulation of lower-level cognitive and manipulative functions as well as for the study of various forms of knowledge representation and automatic theory formation. These concepts will be common in some form to all "intelligent" systems and must be more fully developed from their present primitive state. Mass spectrometry is ideal as a milieu for this research in that it has tremendous practical importance to medicine, is sufficiently complex to challenge the human intellect, and is structured to an extent amenable to computer program formulation within the current state-of-the-art.

COLLABORATIVE ARRANGEMENTS

COLLABORATIVE ARRANGEMENTS

This project is an interdisciplinary research effort involving day-to-day collaboration between Professor J. Lederberg (Department of Genetics), Professor C. Djerassi (Department of Chemistry), Professor E. Feigenbaum (Department of Computer Science), Professor H. Cann (Department of Pediatrics), Dr. B. Buchanan (Computer Science), Dr. A. Duffield (Genetics), Dr. D. Smith (Chemistry), Dr. N. Sridharan (Computer Science), Dr. S. Hammerum (Chemistry), and the Instrumentation Research Laboratory of the Department of Genetics. We are also soliciting additional participation of clinical research interests of the Departments of Medicine and Psychiatry as well as other members of the Department of Genetics (Professors Cavalli-Sforza and Herzenberg). The proximity of these people and facilities in a medical environment offers a highly unique opportunity for collaborative interaction.

FACILITIES AVAILABLE

FACILITIES AVAILABLE

We will derive much of the clinically significant material for analysis from patients in the Premature Research Center and the Clinical Research Center of the Department of Pediatrics at Stanford. Analyses will be performed on existing gas chromatograph and mass spectrometer instrumentation. We have available a GC-coupled Finnigan 1015 quadrupole instrument in the Department of Genetics and a GC-coupled Varian-MAT 711 instrument in the Department of Chemistry. Also available in the Department of Chemistry are MS-9 and Varian-MAT CH-4 instruments.

We will derive our computing resources from existing PDP-11/20 mini-computer systems which interface the mass spectrometer instruments as well as from the ACME follow-on 370/158 computer at Stanford for data reduction and graphics support. Artificial intelligence program development will be carried out on the Stanford Computation Center IBM 360/67 and machines available over the ARPA computer network. GC/MS data will be interfaced to these programs through standard communication links.

HUMAN SUBJECTS

HUMAN SUBJECTS

As a part of this research project, GC/MS analysis techniques will be applied to human body fluids in collaboration with clinical investigators and blood and urine specimens will be collected from human subjects. Collection of VOIDED URINE SPECIMENS presents no risk to the patient. Collection of 5-10 ml of blood by venepuncture is a procedure attended by minimal risk; infection is a remote possibility, especially from deep venepuncture (e.g. femoral tap). However, superficial veins are usually used in children, and even infants. It is only the occasional infant that requires a femoral tap and this procedure would be deferred for this project unless the specimen was essential for diagnosis.

BUDGETS AND JUSTIFICATION

In the following budget estimates, the abbreviations listed below are used to denote departmental affiliation or professional specialty:

G - Genetics

CS - Computer Science

Ch - Chemistry

E - Electrical Engineering

BUDGET - PART A

APPLICATIONS OF ARTIFICIAL INTELLIGENCE

TO MASS SPECTROMETRY

PRIVILEGED COMMUNICATION | SECTION II | SUBSTITUTE THIS PAGE FOR DETAILED BUDGET PAGE

SUBSTITUTE
DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

PERIOD COVERED: FROM 5/1/74 THROUGH 4/30/75

GRANT NUMBER

1. PERSONNEL (List all personnel engaged on project) NAME (Last, first, initial)		TITLE OF POSITION	TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents) TOTAL
Lederberg, Joshua	G	Principal Investigator or Program Director	4	PART A
Feigenbaum, Edward A (1)	CS	Co-Principal Invest.	10	
Buchanan, Bruce G. (1,2)	CS	Associate Invest.	50	
Duffield, Alan	Ch	Associate Invest.	25	
Smith, Dennis	Ch	Research Associate	100	
Hammerum, Steen	Ch	Research Associate	50	
Sridharan, Natesa	CS	Research Associate	50	
Reiss, Steve	CS	Computer Programmer	50	
Hjelmeland, Larry	CS	Research Assistant	100	
Masinter, Larry	CS	Research Assistant	50	
Stefik, Mark	CS	Research Assistant	50	
Wharton, Kathy		Admin. Assistant	25	
Larson, Dee		Secretary	25	

(1) See Budget Notes
(2) In first year only 9/1/74-4/30/75 covered

TOTAL →		$ 80,624
2. CONSULTANT COSTS (Include Fees and Travel)		$ 1,100
3. EQUIPMENT (Itemize)		$ –
4. SUPPLIES — Office supplies		$ 350
5. STAFF TRAVEL (See Instructions)	a. DOMESTIC	$ 1,400
	b. FOREIGN	$
6. PATIENT COSTS (Separate Inpatient and Outpatient)		$ –
7. ALTERATIONS AND RENOVATIONS		$ –

8. OTHER EXPENSES (Itemize per instructions)

Telephone, postage, etc.	$ 200
Publication costs	700
Computer terminal rent	3,200
Computer usage costs	36,000

$ 40,100

9.			Subtotal – Items 1 thru 8 →	$ 123,574
FOR TRAINING GRANTS ONLY	10. TRAINEE EXPENSES (See Instructions)			
	a. STIPENDS	PREDOCTORAL	No. Proposed ____	$
		POSTDOCTORAL	No. Proposed ____	$
		OTHER (Specify)	No. Proposed ____	$
		DEPENDENCY ALLOWANCE		$
			TOTAL STIPEND EXPENSES →	$
	b. TUITION AND FEES			$
	c. TRAINEE TRAVEL (Describe)			$
	11.		Subtotal – Trainee Expenses →	$
12. TOTAL DIRECT COST (Add Subtotals, Items 9 and 11, and enter on Page 1) →				$ 123,574

Part A

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)

DESCRIPTION	1ST PERIOD (SAME AS DETAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED (This application only)					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	80,624	95,175	100,320				
CONSULTANT COSTS *(Include fees, travel, etc.)*	1,100	1,200	1,300				
EQUIPMENT	-	-	-				
SUPPLIES	350	400	450				
TRAVEL – DOMESTIC	1,400	1,600	1,800				
TRAVEL – FOREIGN							
PATIENT COSTS	-	-	-				
ALTERATIONS AND RENOVATIONS	-	-	-				
OTHER EXPENSES	40,100	45,450	50,000				
TOTAL DIRECT COSTS	123,574	143,825	153,870				

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Enter on Page 1, Item 4)* ⟶ $ 421,269

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

See attached budget justification notes.

BUDGET - PARTS B (i) AND B (ii)

MASS SPECTROMETER DATA SYSTEM DEVELOPMENT

AND

ANALYSIS OF THE CHEMICAL CONSTITUENTS OF BODY FLUIDS

PRIVILEGED COMMUNICATION

SECTION II SUBSTITUTE THIS PAGE FOR DETAILED BUDGET PAGE

SUBSTITUTE
DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

PERIOD COVERED: FROM 5/1/74 THROUGH 4/30/75

GRANT NUMBER

1. PERSONNEL (List all personnel engaged on project) NAME (Last, first, initial)		TITLE OF POSITION	TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents) TOTAL
Lederberg, Joshua	G	Principal Investigator or Program Director	3	PART B (i) and (ii)
Duffield, Alan	Ch	Associate Investig.	25	
Pereira, Wilfred	Ch	Research Associate	50	
Summons, Roger	Ch	Post Doctoral Fellow	100	
Rindfleisch, Thomas	E	Research Associate	100	
Veizades, Nicholas	E	Research Engineer	100	
Reynolds, Walter	E	Research Engineer	20	
Tucker, Robert	CS	Computer Programmer	75	
Wegmann, Annemarie	Ch	Sr.Research Assist.	100	
Steed, Ernest	E	Research Engineer	10	
Pearson, Dale	E	Electronics Tech.	60	
DeFrancisci, Richard		Machinist	20	
Allan, Muriel		Secretary	25	

TOTAL →	$ 139,830
2. CONSULTANT COSTS (Include Fees and Travel)	$ -
3. EQUIPMENT (Itemize) Computer Terminal	$ 3,000 *
4. SUPPLIES Office supplies-$750; chemicals,glassware,and lab apparatus-$2,500; GC supplies (gases,phases,columns,etc.)-$950; dry ice and liq.nitrogen-$1,500; electronic supplies and parts-$3,500;GC/MS data recording media-$2,100; mini-computer supplies-$1,500; mass spec. repairs and parts-$7,600	$ 20,400
5. STAFF TRAVEL (See Instructions) a. DOMESTIC 1 east coast ($500); 1 mid-west ($350); 1 west coast ($150)	$ 1,000
5. STAFF TRAVEL (See Instructions) b. FOREIGN	$ -
6. PATIENT COSTS (Separate Inpatient and Outpatient)	$ -
7. ALTERATIONS AND RENOVATIONS Mass spectrometer laboratory air conditioning and power modifications	$ 2,500
8. OTHER EXPENSES (Itemize per instructions) Telephone and data communications - $1,200; Publication costs - $1,000; Mini-computer maintenance contract - $4,600; computing costs from ACME follow-on - $64,000	$ 70,800
9. Subtotal – Items 1 thru 8 →	$ 237,530

FOR TRAINING GRANTS ONLY

10. TRAINEE EXPENSES (See Instructions)			
a. STIPENDS	PREDOCTORAL	No. Proposed ____	$
	POSTDOCTORAL	No. Proposed ____	$
	OTHER (Specify)	No. Proposed ____	$
	DEPENDENCY ALLOWANCE		$
TOTAL STIPEND EXPENSES →			$
b. TUITION AND FEES			$
c. TRAINEE TRAVEL (Describe)			$
11. Subtotal – Trainee Expenses →			$

12. TOTAL DIRECT COST (Add Subtotals, Items 9 and 11, and enter on Page 1) →	$ 237,530

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)

DESCRIPTION	1ST PERIOD (SAME AS DETAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED *(This application only)*					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	139,830	148,066	156,775				
CONSULTANT COSTS *(Include fees, travel, etc.)*	–	–	–				
EQUIPMENT	3,000	3,000	3,000				
SUPPLIES	20,400	21,050	22,250				
TRAVEL – DOMESTIC	1,000	1,000	1,000				
TRAVEL – FOREIGN							
PATIENT COSTS	–	–	–				
ALTERATIONS AND RENOVATIONS	2,500	–	–				
OTHER EXPENSES	70,800	75,000	79,500				
TOTAL DIRECT COSTS	237,530	248,116	262,525				

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Enter on Page 1, Item 4)* ⟶ **$** 748,171

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

See attached budget justification.

BUDGET - PART C

EXTENSION OF THE THEORY OF

MASS SPECTROMETRY BY COMPUTER

PRIVILEGED COMMUNICATION | SECTION II | SUBSTITUTE THIS PAGE FOR DETAILED BUDGET PAGE

SUBSTITUTE
DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

PERIOD COVERED: FROM 5/1/74 THROUGH 4/30/75

GRANT NUMBER:

1. PERSONNEL (List all personnel engaged on project) NAME (Last, first, initial)		TITLE OF POSITION	TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents) TOTAL
Lederberg, Joshua	G	Principal Investigator or Program Director	3	PART C
Feigenbaum, Edward A.(1)	CS	Co-Principal Invest.	10	
Buchanan, Bruce G.(1,2)	CS	Associate Invest.	50	
Sridharan, Natesa	CS	Research Associate	50	
Hammerum, Steen	Ch	Research Associate	50	
White, William	CS	Computer Programmer	50	
Farrell, Carl	CS	Research Assistant	100	
Wharton, Kathy		Admin. Assistant	25	
Larson, Dee		Secretary	25	

(1) See budget notes
(2) Covers 9/1/74-4/30/75 in year 1

TOTAL →		$ 48,521
2. CONSULTANT COSTS (Include Fees and Travel)		$ -
3. EQUIPMENT (Itemize)		$ -
4. SUPPLIES		$ 350
5. STAFF TRAVEL (See Instructions)	a. DOMESTIC	$ 1,400
	b. FOREIGN	$
6. PATIENT COSTS (Separate Inpatient and Outpatient)		$ -
7. ALTERATIONS AND RENOVATIONS		$ -
8. OTHER EXPENSES (Itemize per instructions)		
Telephone, postage, etc.	$ 200	
Publication costs	700	
Computer terminal rental	1,600	
Computer usage	21,000	
		$ 23,500
9. Subtotal – Items 1 thru 8 →		$ 73,771

FOR TRAINING GRANTS ONLY	10. TRAINEE EXPENSES (See Instructions)			
	a. STIPENDS	PREDOCTORAL No. Proposed ____	$	
		POSTDOCTORAL No. Proposed ____	$	
		OTHER (Specify) No. Proposed ____	$	
		DEPENDENCY ALLOWANCE	$	
	TOTAL STIPEND EXPENSES →			$
	b. TUITION AND FEES			$
	c. TRAINEE TRAVEL (Describe)			$
	11. Subtotal – Trainee Expenses →			$
12. TOTAL DIRECT COST (Add Subtotals, Items 9 and 11, and enter on Page 1) →				$ 73,771

GPO 930-791

SECTION II – PRIVILEGED COMMUNICATION

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)

DESCRIPTION		1ST PERIOD (SAME AS DETAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED *(This application only)*					
			2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS		48,521	61,194	64,655				
CONSULTANT COSTS *(Include fees, travel, etc.)*		–	–	–				
EQUIPMENT		–	–	–				
SUPPLIES		350	400	450				
TRAVEL	DOMESTIC	1,400	1,600	1,800				
	FOREIGN							
PATIENT COSTS		–	–	–				
ALTERATIONS AND RENOVATIONS		–	–	–				
OTHER EXPENSES		23,500	27,650	30,450				
TOTAL DIRECT COSTS		73,771	90,844	97,355				

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Enter on Page 1, Item 4)* ⟶ $ 261,970

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

See attached budget justification notes.